



Positive Quality Intervention: Ibrutinib (Imbruvica®) Management in Pediatric Patients

Description: This document will review the appropriate management and clinical interventions with ibrutinib for pediatric patients with chronic Graft Versus Host Disease (cGVHD).

Background: Ibrutinib is a small molecule that acts as a potent, irreversible inhibitor of Bruton’s Tyrosine Kinase (BTK), a key component of the B-cell receptor and cytokine receptor signaling pathway. BTK inhibition is vital for decreased B-cell surface receptor activation. By disrupting these pathways, ibrutinib is able to treat cGVHD after failure of one or more lines of systemic therapy. The iMAGINE study evaluated the PK, safety, and efficacy of ibrutinib in patients ≥ 1 to 22 years old with treatment-naïve (TN) or relapsed/refractory (R/R) moderate/severe cGVHD. Plasma concentration-time profiles for ibrutinib 240 mg/m² (recommended pediatric equivalent) were comparable to those observed in adults with cGVHD at a dose of 420 mg/day. Safety was consistent with the known profile of ibrutinib in cGVHD. The overall response rate by 24 weeks was 64%, including 83% for the TN subgroup and 60% for R/R. Among 46 responders (median follow-up, 20 months; range, 2 to 32 months), 12- month duration of response for each subgroup was 60% (95% confidence interval (CI), 25% to 83%) in TN patients and 58% (95% CI, 35% to 75%) in R/R patients.¹ Management of both medication dosing and adverse effects are prime examples of key areas for additional intervention opportunities for improved patient health outcomes within the medically integrated team.

PQI Process: Upon receiving new ibrutinib prescription in pediatric patients

- Confirm appropriate indication and dosing
cGVHD 420 mg (>12 yo) or 240 mg/m² (1-12 yo) by mouth once daily (max 420 mg)

| | Recommended dose to achieve 240 mg/m ² | |
|-----------------------------|---|--------------------------------------|
| BSA (m ²) Range | Dose (mg) Capsules/Tablets | Dose (mL) Oral Suspension (70 mg/mL) |
| > 0.3 to 0.4 | - | 1.2 mL |
| > 0.4 to 0.5 | - | 1.5 mL |
| > 0.5 to 0.6 | - | 1.9 mL |
| > 0.6 to 0.7 | - | 2.2 mL |
| > 0.7 to 0.8 | 210 mg | 2.6 mL |
| > 0.8 to 0.9 | 210 mg | 2.9 mL |
| > 0.9 to 1 | 210 mg | 3.3 mL |
| > 1 to 1.1 | 280 mg | 3.6 mL |
| > 1.1 to 1.2 | 280 mg | 4 mL |
| > 1.2 to 1.3 | 280 mg | 4.3 mL |
| > 1.3 to 1.4 | 350 mg | 4.6 mL |
| > 1.4 to 1.5 | 350 mg | 5 mL |
| > 1.5 to 1.6 | 350 mg | 5.3 mL |
| > 1.6 | 420 mg | 6 mL |

IMPORTANT NOTICE: NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not provide individual medical advice, and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual’s sole responsibility to seek guidance from a qualified healthcare professional. *Updated 5.13.24*

- Verify pregnancy status in females of reproductive potential and ensure use of effective contraception during treatment and for 1 month after the last dose
- Monitor CBC at baseline, monthly and as clinically necessary
- Monitor CMP monthly and as clinically necessary
 - Dose modifications are needed in patients with total bilirubin > 1.5-3 x upper limit of normal (unless of non-hepatic origin or due to Gilbert's syndrome)
- Blood pressure and ECG/ECHO at baseline (patients with cardiac history/risk factors) and periodically as clinically necessary
- Evaluate patients on anticoagulation, including low-dose aspirin, for bleeding risk
- Hold 3 days pre/post minor surgical procedures and pre/post 7 days for major surgical procedures
- Consider Pneumocystis Jirovecii Pneumonia (PJP) prophylaxis

Adverse Effects

| Adverse Reaction | All Grades (%) |
|------------------------|----------------|
| Diarrhea | 28 |
| Musculoskeletal Pain | 30 |
| Nausea and/or Vomiting | 19 |
| Abdominal Pain | 23 |
| Bruising | 13 |
| Rash | 19 |
| Hemorrhage | 17 |
| Sinus tachycardia | 11 |

| Adverse Reaction | Grade ≥3 (%) |
|------------------|--------------|
| Fever | 11 |
| Infections | 4-13 |
| Cytopenias | 4-13 |
| Hypertension | 4 |
| Osteonecrosis | 9 |
| Stomatitis | 9 |
| Hypokalemia | 6 |
| ALT increased | 2 |

Recommended Dose Modifications for Toxicity Occurrences:

| Adverse Reaction | Occurrence | cGVHD (>12 yo) After Recovery | Dose Modification cGVHD (1-12 yo) After Recovery |
|---|------------|-------------------------------|--|
| Grade 3 Cardiac Arrhythmias | First | Restart at 280 mg daily* | Restart at 160 mg/m ² daily* |
| | Second | Discontinue | Discontinue |
| Grade 3/4 Cardiac Failure, Grade 4 Cardiac Arrhythmia | First | Discontinue | Discontinue |
| Grade 2 Cardiac Failure, Other Grade 3/4 Non-Hematological Toxicity, Grade 3/4 Neutropenia with Infection/Fever, Grade 4 Hematologic Toxicity | First | Restart at 280 mg daily* | Restart at 160 mg/m ² daily* |
| | Second | Restart at 140 mg daily* | Restart at 80 mg/m ² daily* |
| | Third | Discontinue | Discontinue |

* Benefit-risk should be evaluated before resuming treatment

Drug Interactions:

- **CYP3A4 Inducers (Strong):** May decrease the serum concentration of ibrutinib (e.g. carbamazepine, rifampin, phenytoin, St. John's Wort)
 - Risk: Avoid combination
- **CYP3A4 Inhibitors (Strong):** May increase the serum concentration of ibrutinib.
 - Management: Avoid concomitant use of ibrutinib and strong CYP3A4 inhibitors; if a strong CYP3A4 inhibitor must be used short-term (e.g. anti-infectives for 7 days or less), interrupt ibrutinib therapy until the strong CYP3A4 inhibitor is discontinued (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin)
 - Avoid grapefruit and Seville oranges during ibrutinib treatment
 - Risk: Avoid combination
- **Posaconazole and Voriconazole:** Dose modifications are recommended based on dose and formulation of the inhibitor
- **Vaccines (Live):** Immunosuppressants may enhance the adverse/toxic effect of vaccines and may diminish the therapeutic effect of vaccines
 - Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants
 - Risk: Avoid combination
- **Warfarin and anticoagulation:** Increased bleeding risk: Consider risk versus benefit

Patient-Centered Activities:

- Provide the attached pediatric patient education sheet
- Ensure patients understand the formulation prescribed and how to take their dose
 - Varying dosage forms: capsules: 70 mg, 140 mg; tablets: 140 mg, 280 mg, 420 mg, 560 mg; suspension: 70 mg/mL (108 mL)
- Administer orally once daily at approximately the same time each day with a glass of water
- Swallow whole; do not break, crush, chew with tablets and capsules
- Suspension
 - With first use document 60 days from opening as the discard date on the container
 - Shake well before use
 - Attached bottle adapter should not be removed and may be wiped with a disposable tissue
 - Use provided oral syringes to measure dose and administer along inside of cheek in the mouth; dose may need to be split between multiple syringes; after use, rinse oral syringe with water only and let air dry
 - If cannot read markings throw away and call 1-877-877-3536 for new syringes
 - Store bottle at 2°C to 25°C (36°F to 77°F)
- If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day
- Proper sign/symptom monitoring
 - If any abnormal bruising or bleeding especially those on anticoagulation or aspirin
 - If there are any new medications (assess for risk of QT prolongation or drug-drug interactions)
 - Report any signs/symptoms of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema
 - Report any signs/symptoms of infection (fever, chills, weakness, confusion)
 - Evaluate if patients have missed any doses between cycles to determine if interventions are needed such as reminders, calendars, etc
- Patient Assistance: [NCODA Financial Assistance Tool](#)

References:

1. Carpenter PA, Kang HJ, Yoo KH, et al. Ibrutinib treatment of pediatric chronic graft-versus-host-disease: primary results from the phase ½ iMAGINE study. *Transplant Cell Ther* 2022; 28(11): 771.e1-771.e10.
2. [Imbruvica® \(ibrutinib\) \[package insert\]](#).

IBRUTINIB PEDIATRIC EDUCATION



IBRUTINIB

Name of your child's medication

Generic Name – Ibrutinib (i-BROO-tih-nib)

Brand Name – Imbruvica (im-BROO-vih-kuh)

Approved uses

Ibrutinib is used to treat children who have received a bone marrow transplant and now have chronic graft-versus-host disease (cGVHD).

Dose and schedule

Taking ibrutinib as instructed is important to allow your child's treatment to be as effective as possible, so here are some key points to remember.

- Your child's dose may vary, but ibrutinib is to be taken by mouth at a scheduled time once a day.
- Ibrutinib can be taken with or without food, but should be taken at the same time each day.
- Ibrutinib is available as regular tablets, capsules, or a suspension. The regular tablets and capsules should be taken whole and not opened, crushed, cut, or dissolved. If your child is unable to swallow ibrutinib, talk to your child's care team or pharmacist for possible options.
- If you miss a dose of ibrutinib, give your child's missed dose as soon as possible on the same day and then return to your child's normal schedule the next day. **Do not** take an extra dose or two doses at one time to make up for the missed dose. Simply take your child's next dose at the regularly scheduled time.
- Be sure to write down if you miss a dose and let your child's care team know about any missed doses.

Drug and food interactions

- Ibrutinib has many drug interactions, please inform your child's care team of all prescription medications, over-the-counter medications, vitamins, and herbal products.
- Grapefruit or grapefruit juice and Seville oranges (often found in marmalades) may interact with ibrutinib; avoid eating or drinking these during treatment with ibrutinib.
- Talk with your child's care team or pharmacist before taking new medications or supplements, or receiving any vaccines.

Storage and handling

Handle ibrutinib with care. Just like when chemotherapy is given into the vein, this drug can be toxic, and exposure of the drug to others should be limited.

- Store ibrutinib capsules and tablets at room temperature (68°F-77°F) in a dry location away from light.
- Store ibrutinib suspension at 36°F–77°F. Do not use if carton seal is broken or missing as suspension should be dispensed in original container. Discard unused oral suspension remaining 60 days after initial opening of bottle along with oral syringe(s) used to give the medication. Please note the opening date on the bottle.
- Keep ibrutinib out of reach of children and pets.
- Leave ibrutinib in the provided packaging until it is ready to be taken.
- Family member or caregiver giving the ibrutinib need to follow these steps for capsules/tablets.

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1. Wash hands with soap and water.
 2. Put on gloves to avoid touching the medication. (Gloves are not necessary if the child is able to give the drug to themselves.)
 3. Gently transfer the ibrutinib from its package to a small medicine or other disposable cup.
 4. Administer the medicine immediately by mouth with water.
 5. Remove gloves and do not use them for anything else.
 6. Throw gloves and medicine cup in household trash.
 7. Wash hands with soap and water.
- If a daily pill box or pill reminder is used, a separate one should be used for ibrutinib. **Do not** mix other medications into the box with ibrutinib. The caregiver filling the box or reminder should wear gloves (gloves are not necessary if your child is filling the box or reminder). When empty, the box or reminder should be washed with soap and water before refilling. Be sure to wash hands with soap and water after the task is complete, whether or not gloves are worn.
 - Family member or caregiver giving the ibrutinib need to follow these steps for suspension.
 1. Wash hands with soap and water.
 2. Put on gloves to avoid touching the medication.
 3. Gather and check supplies.
 - Check the prescribed dose in milliliters (mLs) and find this marking on the oral syringe provided with the medication.
 - The dose may need to be split into multiple syringes if the dose is more than the markings on the oral syringe.
 4. Record or check the discard date.
 5. Shake the bottle well before each use.
 6. Remove cap from bottle and do not remove adapter. If there is fluid on top of the adapter, it can be wiped clean with a disposable tissue.
 7. Make sure the oral syringe(s) are clean and dry before use. Push the plunger all the way down. Gently insert the tip of the syringe into the adapter. Turn the assembled bottle and syringe upside down.
 8. Slowly pull the syringe plunger down, past the number of mLs for the prescribed dose.
 9. Check for air bubbles. To remove air bubbles and adjust to the prescribed dose in mLs. Hold the syringe and tap the sides to send bubbles to the tip. With the syringe attached to the bottle push the plunger up to remove the air bubbles from the top. After bubbles are removed, push the plunger up until the top of the colored plunger is even with the markings on the syringe for the prescribed dose.
 10. Turn the assembled bottle upright. Hold the middle of the syringe and carefully remove it from the bottle and place the bottle aside.
 11. Place the tip of the syringe along the inside of the cheek and slowly push the plunger all the way in to take or give the entire dose. Repeat with the second syringe if needed to complete the prescribed dose.
 12. Recap the bottle and make sure the bottle is tightly closed between each use.
 13. To rinse the oral syringe(s) remove the plunger from the syringe. Rinse the plunger and the syringe with water only and allow the syringe to air dry. Store the syringe(s) in a clean, dry place. Do not clean the syringe with soap or in the dishwasher.
 14. Remove gloves and do not use them for anything else.
 15. Throw gloves in household trash.
 16. Wash hands with soap and water.
 - If you have any unused ibrutinib, **do not** throw it in the trash and **do not** flush it down the sink or toilet. Talk to your child's care team or pharmacist about proper disposal of ibrutinib.
 - If you are traveling, put your child's ibrutinib in a sealed plastic bag. Ask your child's pharmacist if any additional travel precautions are needed.

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Handling body fluids and waste

Since ibrutinib remains in your child's body for several days after it is taken, some of the drug may be present in urine, stool, sweat, or vomit. Once your child has started to take ibrutinib, it is important to know the following instructions every day for as long as your child's treatment lasts. This is to keep your child, yourself, loved ones, and the environment as safe as possible.

- Pregnant women should avoid touching anything that may be soiled with body fluids from the patient.
- Toilet and septic systems:
 - Your child may use the same toilet, septic tank, and/or sewer that you usually use. If you have a low-flow toilet, close the lid and flush twice to ensure all waste has been discarded.
 - If the toilet or toilet seat becomes soiled with urine, stool, or vomit, clean the surfaces before other people use the toilet.
 - Wash your child's hands with soap and water after using the toilet.
- If your child needs a bedpan, caregivers need to wear gloves to assist with cleanup and to wash the bedpan with soap and water every day.
- If your child is not fully potty trained, use a disposable pad with a plastic back, a diaper, or a sheet to absorb body waste.
- Wash any skin that has been exposed to body waste or ibrutinib with soap and water.
- Linens or clothing that are soiled with body fluids or body waste should be washed separately from other linens and clothing. If you do not have a washer, place the soiled linens in a plastic bag until they can be washed.
- Wash hands with soap and water after touching linens or clothing that may be soiled with body fluids.

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The common side effects that have been known to happen in patients taking ibrutinib are listed in the left side of this table. Your child **MAY NOT** experience these side effects. Options to help manage any side effects that do occur are included on the right side of this table. These should be discussed with your child's care team. If you experience any side effect you cannot manage or that is not listed here, contact your child's care team.

| Side Effect | Management |
|---|---|
| <p>Decreased platelet count and increased risk of bleeding</p> | <p>Your child's platelets should be monitored by a simple blood test. When they are low, you may bruise or bleed more easily than usual.</p> <ul style="list-style-type: none"> • Use caution to avoid bruises, cuts, or burns. • Blow nose gently and do not pick nose • Brush teeth gently with a soft toothbrush and maintain good oral hygiene • Use a nail file instead of a nail clippers <p>Call your child's care team if you have bleeding that won't stop. Examples include:</p> <ul style="list-style-type: none"> • A bloody nose that bleeds for more than 5 minutes despite pressure • A cut that continues to ooze despite pressure • Gums that bleed excessively when flossing or brushing <p>Seek medical help immediately if your child experiences any severe headaches, blood in your child's urine or stool, coughing up blood, or prolonged and uncontrollable bleeding.</p> <p>Your child may need to take a break or "hold" medication for medical or dental procedures. Talk to your child's care team or dentist before any scheduled procedures.</p> |
| <p>Decreased white blood cells (WBCs) and increased risk for infection</p> | <p>Your child's WBCs should be monitored by a simple blood test. When WBCs are low, your child is at a greater risk of having an infection. Take the following precautions to protect from infections.</p> <ul style="list-style-type: none"> • Wash your child's hands often, especially before eating and after using the bathroom. • Avoid crowds and people with fevers, flu, or other infection. • Bathe regularly to keep good personal hygiene. <p>Contact your child's care team if you experience any signs or symptoms of an infection such as:</p> <ul style="list-style-type: none"> • Fever (temperature more than 100.4°F or 38°C) • Chills • Sore throat • Burning with urination • Unusual tiredness • A sore that becomes red, is draining, or does not heal <p>Check with your child's care team before taking any medicine for a fever or chills.</p> |
| <p>Diarrhea (loose and/or urgent bowel movements)</p> | <p>Monitor how many bowel movements your child has each day.</p> <ul style="list-style-type: none"> • Drink 8-10 glasses of water/fluid each day unless your child's care team has instructed you to limit your child's fluid intake due to some other health problem • Eat small, frequent meals throughout the day rather than a few large meals • Eat bland, low-fiber foods (such as bananas, applesauce, potatoes, chicken, rice, and toast) |

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|---|---|
| | <ul style="list-style-type: none"> • Avoid high fiber foods, such as raw vegetables, raw fruits, and whole grains • Avoid foods that cause gas, such as broccoli and beans • Avoid lactose-containing foods, such as yogurt and milk • Avoid spicy, fried, and greasy foods <p>Contact your child’s provider if any of the following occur:</p> <ul style="list-style-type: none"> • The number of bowel movements you have in a day increases by 4 or more • Your child feels dizzy or lightheaded <p>Your child’s care team may recommend an over-the-counter medication called loperamide (Imodium®) to help with your child’s diarrhea, but talk to your child’s care team before starting this medication.</p> |
| Fatigue | <p>Your child may be more tired than usual or have less energy.</p> <ul style="list-style-type: none"> • Stay as active as possible, but know it is okay to rest as needed. • Try to do some activity every day. • Plan your child’s activities, and do them at a time of day when you feel a bit more energetic. |
| Respiratory tract infection | <ul style="list-style-type: none"> • Wash your child’s hands often, especially before eating and after using the bathroom • Avoid people with fevers, flu, or other infections • Maintain good personal hygiene • Report symptoms of a respiratory infection like a cough sneezing, runny nose, fever, and scratchy or sore throat to your child’s provider |
| Decreased hemoglobin, part of the red blood cells that carry iron and oxygen | <p>Your child’s hemoglobin should be monitored by a simple blood test. When your child’s hemoglobin is low, you may notice that your child get tired or fatigued more easily.</p> <ul style="list-style-type: none"> • Try to get 7 to 8 hours of sleep per night • Find a balance between “work/school/play” and “rest” • Stay as active as possible, but know that it is okay to rest as needed, too • You might notice that you are more pale than usual <p>Let your child’s care team know right away if you experience:</p> <ul style="list-style-type: none"> • Shortness of breath • Dizziness • Palpitations |
| Muscle or joint pain or weakness | <ul style="list-style-type: none"> • Keep a diary of your child’s pain, including a description of when and where the pain is occurring, what it feels like, and how long it lasts • Stay as active as possible, but know that it is okay to rest as needed, too • Tell your child’s care team if pain interferes with your child’s activity <p>If the pain or weakness bothers you, ask your child’s provider what you may use to help with this discomfort. Take only pain medication that has been prescribed or recommended by your child’s care team.</p> |
| Fluid retention or swelling | <ul style="list-style-type: none"> • Do not stand for long periods of time • Keep your child’s legs elevated when sitting or lying down • Avoid eating salty foods, which can increase swelling • Avoid wearing tight-fitting clothing and shoes • Weigh your child daily |

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|---------------------------|---|
| | <p>Contact your child's care team if you notice:</p> <ul style="list-style-type: none">• Swelling in the hands, feet, or legs• Shortness of breath• Weight gain of 2-5 pounds or more in a week |
| Nausea or vomiting | <ul style="list-style-type: none">• Eat and drink slowly• Drink 8-10 glasses of water/fluid each day unless your child's care team has instructed you to limit your child's fluid intake• Eat small, frequent meals throughout the day rather than a few large meals• Eat bland foods; avoid spicy, fried, and greasy foods• Avoid vigorous exercise immediately after eating• Don't lay down immediately after eating• Avoid strong odors <p>Let your child's provider know if you experience nausea or vomiting.</p> <p>Your child's provider may prescribe medication to help with the nausea or vomiting.</p> |

Serious side effects

Call your child's doctor or get medical help if any of these side effects or any other side effects that bother your child do not go away:

- Constipation, diarrhea, stomach pain, upset stomach, throwing up, or decreased appetite
- Mouth irritation or mouth sores
- Headache
- Feeling dizzy, tired or weak
- Bone, joint, or muscle pain
- Muscle spasm
- Anxiety
- Signs of a common cold
- Dry eyes
- More tears
- Trouble sleeping
- Weight loss

Serious side effects can occur, and your child's care team should be contacted right away. These include:

- Infection: watch for fever or other signs of infection.
- Low blood counts: watch for signs of bleeding or fatigue.
- High blood pressure: watch for signs of dizziness, headache, weight gain or swelling in arms or legs
- Irregular heartbeats: watch for signs of fast, slow or abnormal heart beats.
- Allergic reaction: watch for signs of skin rash, hives, itching, wheezing, tightness in chest or throat, trouble breathing, swelling of the mouth, face, lips, tongue or throat.
- There is small risk of developing a second cancer years or months after taking ibrutinib. Talk to your child's provider about this risk.

If your child experience ANY uncontrolled side effect, call your child's physician/health care center immediately:

(INSTITUTIONAL CONTACT INFO)

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Pregnancy, sexual activity, and contraception

- Women should not become pregnant and men should not get a partner pregnant while taking ibrutinib. Males and females of childbearing age and potential should use effective contraception during therapy and for a minimum of 1 month after the last dose of ibrutinib.
- Do not breastfeed while taking ibrutinib and for 1 month after the last dose of ibrutinib.
- Please inform your child's care team if your child becomes pregnant.
- It is safe to hug and kiss. Special precautions may be needed for sexual activity while on oral chemotherapy, and you are encouraged to ask your child's care team.

Obtaining medication

- Talk with your child's care team about the process for obtaining your child's ibrutinib.

_____(PHARMACY/SPECIALTY PHARMACY CONTACT INFO)

Additional resources

Product website: <https://www.imbruvica.com/>

Product prescribing information: https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing_information.pdf

Product resources: <https://www.imbruvica.com/you-i-support>

Updated – March 22, 2024

Additional instructions
